REMARKS

The final Office Action dated October 18, 2007 ("Office Action") has been carefully reviewed and considered. The specification has been amended to correct clerical errors which Applicants believe help clarify that hydroxypropylmethylcellulose is a neutral, hydrophilic colloid and not a polyelectrolyte. No new matter has been added.

Currently, claims 1-20 and 22 are pending in the present application. Claims 18-20 and 22 have been withdrawn from consideration. Claim 21 has been cancelled. Applicants reserve the right to pursue subject matter recited in the withdrawn and cancelled claims in one or more related applications. Reconsideration of the present application in view of the following remarks is respectfully requested. No new matter has been added.

I. INTERVIEW SUMMARY

Applicants' representatives, Ms. Evangeline Shih and Ms. Janet Fair of Jones Day thank Examiner Blessing M. Fubara of the United States Patent and Trademark Office for the courtesy of the December 3, 2007 telephone interview in connection with the above-identified application ("Interview"). In-house counsel for the assignee, Ms. Lisa White of UPM Pharmaceuticals, Inc., also participated in the Interview. During the Interview, the Office Action was discussed with particular focus on the Examiner's maintenance of her rejection of claims under 35 U.S.C. §102(b) as being anticipated by Cuna *et al.* "Controlled-release liquid suspensions based on ion-exchange particles entrapped within acrylic microcapsules," International Journal of Pharmaceutics 199 (2000), pp 151-158 ("Cuna") and US Patent No. 4,894,239 to Nonomura *et al.* ("Nonomura").

Applicants' representatives restated Applicants' position that neither Cuna nor Nonomura teach or suggest a liquid form controlled release drug formulation that includes, *inter alia,* a dispersion medium comprising a pharmaceutically acceptable polyelectrolyte having the same charge as the electrolytic drug. In particular, Applicants' representatives explained why the paragraphs in Cuna and Nonomura that where specifically cited by Examiner Fubara in the Office Action could not describe a liquid form controlled release drug formulation that includes a dispersion medium comprising a pharmaceutically acceptable polyelectrolyte having the same charge as the electrolytic drug. Applicants' representative pointed out that the cited paragraphs did not teach or suggest a liquid form controlled release drug formulation. Instead, the cited paragraphs disclosed reaction schemes for coating drug-loaded resin beads, an intermediate step used for formulating a controlled

release drug formulation. First, the composition of the intermediate step would be a non-pharmaceutically acceptable composition, and not suitable as a drug formulation. Second, in Cuna, Applicants' representatives explained that even if the intermediate composition were considered a drug formulation, the EUDRAGIT component, which Examiner Fubara suggests is a polyelectrolyte, resides in the dispersed phase, and not in the dispersion medium. As such, there is no polyelectrolyte in the dispersion medium, as required by the claims.

In response, Examiner Fubara raised the issue that in addition to the intermediate compositions, Cuna and Nonomura do actually describe final products that are controlled release drug formulations. Applicants' representatives explained that while Cuna and Nonomura do suggest liquid form controlled release formulations in final form, the end products that are controlled release drug compositions in Cuna and Nonomura also do not include a dispersion medium comprising a pharmaceutically acceptable polyelectrolyte having the same charge as the electrolytic drug.

Examiner Fubara and Applicants' representatives also discussed the compliance of claim 1 with 35 U.S.C. § 112, first paragraph. Applicants' representatives stated that as previously amended, claim 1 is in compliance with 35 U.S.C. § 112, first paragraph, since one of ordinary skill in the art would not use polyelectrolytes associated with Hg and Ag ions since, as taught in US Pat. No. 5, 882,677 to Kupperblatt ("Kupperblatt"), such ions are not medically or pharmaceutically acceptable. Examiner Fubara indicated that if this were the case, she agreed with Applicants' representatives, but reserved the opportunity to verify that Kupperblatt taught that Hg and Ag ions were not medically acceptable.

At the conclusion of the Interview, Examiner Fubara indicated her willingness to reconsider the claims in view of the Interview discussion and the following arguments set forth in more detail below.

II. THE REJECTION OF CLAIMS 1-17 AND 21 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH SHOULD BE WITHDRAWN

Claims 1-17 and 21 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. For the following reasons, Applicants believe that this rejection has been overcome.

A. Claims 1, 8 and 12 Comply With the Written Description Requirement

At pages 3-4 of the Office Action, the Examiner alleges that claims 1, 8 and 12 are directed to the use of polyelectrolytes without identifying the ions associated with the polyelectrolyte and thus, would not lead the artisan away from using polyelectrolytes that are

unsuitable for medical or pharmaceutical use, such as polyelectrolytes associated with Hg and Ag ions. Applicants respectfully disagree.

As discussed in the Interview, claim 1 recites a liquid form controlled release drug composition comprising, *inter alia*, a dispersion medium comprising a *pharmaceutically acceptable* polyelectrolyte and thus, would lead one of ordinary skill in the art away from using polyelectrolytes associated with ions that are not suitable for pharmaceutical compositions. As an example of pharmaceutically unsuitable polyelectrolytes, Examiner cited US Pat. No. 5, 882,677 to Kupperblatt ("Kupperblatt"), which discloses polyelectrolytes associated with Hg or Ag ions and that such ions are not medically acceptable (Office Action at page 3). Thus, unsuitable polyelectrolytes, such as polyelectrolytes associated with Hg or Ag ions are well know in the art (*See* Kupperblatt, col. 5, *ll.* 32-38).

Therefore, Applicants believe that claim 1 and all the claims depending therefrom comply with the written description requirement. Thus, Applicants believe that this rejection has been overcome.

B. Claim 21 Has Been Cancelled

Examiner has also rejected claim 21 as allegedly not complying with the written description requirement of 35 U.S.C. § 112, first paragraph. While Applicants disagree with the Examiner, claim 21 has been cancelled in order to facilitate prosecution. Therefore, this rejection is moot.

Applicants reserve the right to pursue the subject matter of the cancelled claim in one or more related applications.

III. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

A. Cuna *et al.* ("Cuna") Does Not Anticipate Claims 1-3, 5-6, 8, 13-14 and 16 Under 35 U.S.C. § 102(b)

Claims 1-3, 5-6, 8, 13-14 and 16 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Cuna *et al.* "Controlled-release liquid suspensions based on ion-exchange particles entrapped within acrylic microcapsules," International Journal of Pharmaceutics 199 (2000), pp 151-158 ("Cuna"). Applicants disagree.

As discussed during the Interview, claim 1 recites a liquid form controlled release drug composition that includes, *inter alia*, (a) a dispersed phase that includes an ion-exchange matrix drug complex; and (b) a dispersion medium comprising a pharmaceutically acceptable polyelectrolyte having the same charge as the electrolytic drug.

At page 6 of the Office Action, Examiner cites section 2.4 of Cuna and alleges that Cuna discloses a suspension of drug-loaded resin beads in a solution of EUDRAGIT. However, as discussed during the Interview, section 2.4 of Cuna describes the microencapsulation process of the drug-loaded resin beads, which are used in the controlled release drug formulation of Cuna. Thus, the microencapsulation process is only an intermediate step in forming the controlled release liquid formulation of Cuna and the reaction schemes used for microencapsulating the drug-coated resin beads are not liquid form controlled release drug formulations.

During the encapsulation process a dispersed phase, which includes the drug-loaded resin beads, EUDRAGIT and acetone or methylene chloride, is dispersed in a dispersion medium containing water or paraffin and a surfactant. First, this intermediate composition would not be pharmaceutically acceptable, and would be unsuitable as a drug formulation. In particular, acetone or methylene chloride would not be pharmaceutically acceptable excipients and could not be used for administration to patients. Second, even if the reaction schemes of Cuna are considered to be liquid form controlled release drug formulations, the reaction schemes do not include a dispersion medium comprising a pharmaceutically acceptable polyelectrolyte having the same charge as the electrolytic drug. In the reaction schemes disclosed in Cuna, the EUDRAGIT is not in the dispersion medium. The beads, EUDRAGIT and acetone or methylene chloride are contained in the dispersed phase which is then placed into a dispersion medium containing water or paraffin and a surfactant. Therefore, even if the microencapsulation reaction schemes of Cuna were considered liquid form controlled release drug compositions, which they are not, they would not anticipate claim 1 since the reaction schemes of Cuna do not disclose a dispersion medium comprising a pharmaceutically acceptable polyelectrolyte having the same charge as the electrolytic drug, as recited in claim 1.

Moreover, the final product that is the controlled release liquid formulation of Cuna, which includes the coated drug-loaded resin beads, also does not have a dispersion medium comprising a pharmaceutically acceptable polyelectrolyte having the same charge as the electrolytic drug. The controlled release liquid formulation disclosed in Cuna has a dispersed phase that includes coated drug-loaded resin beads and a dispersion medium that includes an aqueous solution of 0.75% w/w of hydroxypropylmethylcellulose (page 154, sec. 2.7). As discussed during the interview and in Applicants' response of August 22, 2007, hydroxypropylmethylcellulose is a neutral polymer and, therefore, is not a pharmaceutically acceptable polyelectrolyte having a charge, let alone, a polyelectrolyte having the same

charge as the cationic drug terbutaline. The fact that hydroxypropylmethylcellulose is a neutral polymer is further supported by the Aldrich Catalog, the relevant excerpt is attached herein as Appendix A. The hydroxypropylmethylcellulose entry in the Aldrich Catalog depicts hydroxypropylmethylcellulose as not carrying a charge, *i.e.* a neutral polymer (Appendix A, Aldrich Catalog, page 836). Thus, Cuna fails to teach or suggest a liquid form controlled release drug composition that includes *inter alia,* an electrolytic drug associated with an ion exchange resin and a dispersion medium comprising a pharmaceutically acceptable polyelectrolyte having the same charge as the electrolytic drug.

Claims 2-3, 5-6, 8, 13-14 and 16 depend from claim 1 and therefore include all the recitations of claim 1. Thus, Applicants believe that claims 1-3, 5-6, 8, 13-14 and 16 are patentable over Cuna and that the Examiner's rejection of claims 1-3, 5-6, 8, 13-14 and 16 should be withdrawn.

B. U.S. Patent No. 4,894,239 to Nonomura *et al.* Does Not Anticipate Claims 1-17 and 21 Under 35 U.S.C. § 102(b)

Claims 1-17 and 21 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 4,894,239 to Nonomura *et al.* ("Nonomura"). Applicants respectfully disagree.

At page 9 of the Office Action, Examiner cites col. 7, *ll.* 55-62 of Nonomura and alleges that Nonomura discloses drug-loaded resin beads dispersed in a solution of EUDRAGIT. As discussed in the Interview, the section of Nonomura that is cited by Examiner is directed to forming coated drug-loaded resin beads, an intermediate to forming the controlled release formulations of Nonomura. As disclosed in Nonomura, cyclohexane is added to drug-loaded resin, EUDRAGIT and chloroform to create a slurry, which is then subjected to spray drying to yield microcapsules (col. 7, *ll.* 55-62). Cyclohexane and chloroform are both unacceptable for pharmaceutical use, making the reaction schemes unacceptable for pharmaceutical use. Therefore, the reaction schemes of Nonomura are not liquid form controlled release drug composition.

Moreover, the controlled release liquid formulation of Nonomura that includes the coated drug-loaded resin beads does not disclose a dispersion medium comprising a pharmaceutically acceptable polyelectrolyte having the same charge as the electrolytic drug. Nonomura only discloses a sustained-release microcapsule preparation that consists of an ion exchange resin containing a drug coated with a water permeable polymer that can be formulated into oral suspensions by dispersing the microcapsules in purified water, surfactant and a syrup, which does not include a polyelectrolyte (Example 9). As such, Nonomura fails

to disclose a liquid form controlled release drug composition that includes *inter alia,* an electrolytic drug associated with an ion exchange resin and a dispersion medium comprising a pharmaceutically acceptable polyelectrolyte having the same charge as the electrolytic drug.

Claims 2-17 depend from claim 1 and therefore include all the recitations of claim 1. Thus, Applicants believe that claims 1-17 are patentable over Nonomura and that Examiner's rejection of claims 1-17 should be withdrawn. As discussed above, claim 21 has been cancelled.

IV. DOUBLE PATENTING REJECTION

Claims 1-17 and 21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-29 of co-pending application nos. 11/150,572 (US2006/0018972) and 11/198,937 (US2006/0134148) to Hollenbeck ("Hollenbeck") in view of WO 95/19184 to Cohen *et al.* ("Cohen").

Applicants disagree with the bases of Examiner's rejection. However, Applicants respectfully request that Examiner hold this provisional double-patenting rejection in abeyance. As the rejection involves pending applications rather than an issued patent, Applicants request that Examiner withdraw the provisional double patenting rejection in the instant application or co-pending Application Nos. 11/150,572 (US2006/0018972) and 11/198,937 (US2006/0134148), which ever is permitted to issue first, and then assert the double patenting rejection in the remaining pending applications, if applicable . *See* M.P.E.P. § 804(I)(B).

Thus, Applicants respectfully request that Examiner hold this provisional double-patenting rejection in abeyance until either this application or any of the co-pending Application Nos. 11/150,572 (US2006/0018972) and 11/198,937 (US2006/0134148) are allowed.

V. CONCLUSION

In light of the above amendments and remarks, it is believed that the claim rejections have been overcome and that the present application is in condition for allowance. Should Examiner not agree with Applicants' position, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application.

Respectfully submitted,

Date: December 18, 2007

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By: Janet E. Fair

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APPENDIX A

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43,500-7 **Hydroxypropyl cellulose** [*9004-64-2*] d 0.500 *Merck Index* **11**,4776 *SI* 500,B,5 — 5g, 100g, 250g
NEW ★ *RTECS#* NF9050000
Powder. Thermoplastic. Average M_n *ca.* 80,000, average M_w *ca.* 10,000. Viscosity (Brookfield, spindle #2, 60 rpm, 10 wt. % in water, 25°C) 150-700 cps

19,188-4 **Hydroxypropyl cellulose** [*9004-64-2*] — 5g, 100g, 250g
★ Powder. Average M_n *ca.* 100,000. Viscosity (Brookfield, spindle #1, 30 rpm, 5 wt. % in water, 25°C) 75-150 cps. Thermoplastic

19,189-2 **Hydroxypropyl cellulose** [*9004-64-2*] — 5g, 100g, 250g
★ Powder. Average M_n *ca.* 370,000. Viscosity (Brookfield, spindle #2, 60 rpm, 2 wt. % in water, 25°C) 150-400 cps. Thermoplastic

19,190-6 **Hydroxypropyl cellulose** [*9004-64-2*] — 5g, 100g, 250g
★ Powder. Average M_n *ca.* 1,000,000. Viscosity (Brookfield, spindle #3, 30 rpm, 1 wt. % in water, 25°C) 1,500-3,000 cps. Thermoplastic

39,069-0 **Hydroxypropyl-α-cyclodextrin** [*99241-24-4*] mp 245° (dec.) $[\alpha]_D^{25}$ + 125° (c = 1, H_2O) — 5g, 25g
Average molar substitution = 0.6

33,259-3 **Hydroxypropyl-β-cyclodextrin** [*94035-02-6*] mp 278° (dec.) $[\alpha]^{25}$ + 139° (c = 1, H_2O) — 5g, 25g, 100g
R&S **1**(1),199I
Average molar substitution = 0.6. Average M.W. 1380

33,260-7 **Hydroxypropyl-β-cyclodextrin** [*94035-02-6*] $[\alpha]^{25}$ + 127° (c = 1, H_2O) — 5g, 25g, 100g
Average molar substitution = 0.8. Average M.W. 1500

38,914-5 **Hydroxypropyl-β-cyclodextrin** [*94035-02-6*] $[\alpha]^{23}$ + 130° (c = 1, H_2O) — 5g, 25g
Average molar substitution = 1.0

39,070-4 **Hydroxypropyl-γ-cyclodextrin** [*99241-25-5*] mp 250° (dec.) $[\alpha]_D^{25}$ + 145° (c = 1, H_2O) — 5g, 25g
Average molar substitution = 0.6

26,854-2 **Hydroxypropyl methacrylate,** 97%, mixture of isomers [*27813-02-1*] — 5mL, 100mL, 1L, 18L
★ $H_2C=C(CH_3)CO_2C_3H_6OH$ FW 144.17 bp 57°/0.5mm n_D^{20} 1.4470 d 1.066 Fp 206°F(96°C)
Beil. 2(4),1532 *FT-NMR* 1(1),1045B *SI* 116,B,9 *Safety* **2**,1957B *R&S* 1(1),755A *IRRITANT*
Mixture of hydroxypropyl and hydroxyisopropyl methacrylates
Inhibited with 1200 ppm hydroquinone monomethyl ether

42,317-3 **Hydroxypropyl methyl cellulose** [*9004-65-3*] *Merck Index* **11**,4777 *SI* 500,C,5 — 25g, 100g
NEW ★ *RTECS#* NF9125000
Average M_n *ca.* 120,000. *ca.* 21 wt. % methoxy, 5 wt. % propylene oxide. Viscosity (Ubbelohde, 2 wt. % solution in water, 20°C) 100,000 cps. D.S. (methoxy) 1.1-1.6. M.S. (propylene oxide) 0.1-0.3

42,318-1 **Hydroxypropyl methyl cellulose** [*9004-65-3*] — 25g, 100g
NEW ★ Average M_n *ca.* 90,000. *ca.* 21 wt. % methoxy, 5 wt. % propylene oxide. Viscosity (Ubbelohde, 2 wt. % solution in water, 20°C) 15,000 cps. D.S. (methoxy) 1.1-1.6. M.S. (propylene oxide) 0.1-0.3

42,320-3 **Hydroxypropyl methyl cellulose** [*9004-65-3*] — 25g, 100g
NEW ★ Average M_n *ca.* 86,000. *ca.* 29 wt. % methoxy, 7 wt. % propylene oxide. Viscosity (Ubbelohde, 2 wt. % solution in water, 20°C) 4,000 cps. D.S. (methoxy) 1.8-2.0. M.S. (propylene oxide) 0.2-0.3

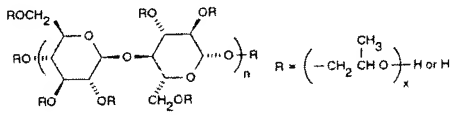
20,032-8 **Hydroxypropyl methyl cellulose** [*9004-65-3*] — 5g, 100g, 250g
★ Powder. Average M_n *ca.* 86,000. *ca.* 29 wt. % methoxy, 7 wt. % propylene oxide. Viscosity (Ubbelohde, 2 wt. % solution in water, 20°C) 4,000 cps. D.S. (methoxy) 1.7-1.9, M.S. (propylene oxide) 0.1-0.2

29,441-1 **Hydroxypropyl methyl cellulose** [*9004-65-3*] — 25g, 100g
★ Average M_n *ca.* 12,000. 21 wt. % methoxy, 5 wt. % propylene oxide. Viscosity (Ubbelohde, 2 wt. % solution in water, 20°C) 80-120 cps. D.S. (methoxy) 1.1-1.6, M.S. (propylene oxide) 0.1-0.3

42,321-1 **Hydroxypropyl methyl cellulose** [*9004-65-3*] — 25g, 100g
NEW ★ Average M_n *ca.* 11,500. *ca.* 29 wt. % methoxy, 7 wt. % propylene oxide. Viscosity (Ubbelohde, 2 wt. % solution in water, 20°C) 50 cps. D.S. (methoxy) 1.8-2.0. M.S. (propylene oxide) 0.2-0.3

42,323-8 **Hydroxypropyl methyl cellulose** [*9004-65-3*] — 25g, 100g
NEW ★ Average M_n *ca.* 10,000. *ca.* 29 wt. % methoxy, 7 wt. % propylene oxide. Viscosity (2 wt. % solution in water, 20°C) 6 cps. D.S. (methoxy) 1.8-2.0. M.S. (propylene oxide) 0.2-0.3

44,275-5 **Hydroxypropyl methyl cellulose** [*9004-65-3*] (METHOCEL® E5) — 25g, 100g
NEW ★ Average M_n *ca.* 10,000. *ca.* 29 wt. % methoxy, 9 wt. % propylene oxide. Viscosity (Ubbelohde, 2 wt. % solution in water, 20°C) 5 cps. D.S. (methoxy) 1.8-2.0. M.S. (propylene oxide) 0.2-0.3



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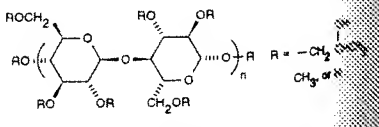


20,032-8

43,520-1 **Hydroxypropyl methyl cellulos**
NEW ★ *SI* 500,A,6 *RTECS#* FJ5954000
ca. 31 wt. % phthalyl, *ca.* 20 wt. %

43,519-8 **Hydroxypropyl methyl cellulos**
NEW ★ *ca.* 24 wt. % phthalyl, *ca.* 22 wt. %

4-(3-Hydroxypropyl)-4-nitro-1,7- trispropanol page 1084

10,306-3 ***N*-(3-Hydroxypropyl)phthalimic**
NEW *SI* 329,E,7

H5,660-6 **4-Hydroxypyrazolo[3,4-*d*]pyrim**
★ mp > 300° *Merck Index* **11**,278
RTECS# UR0785000 *TOXIC*

36,151-8 **1-Hydroxypyrene,** 98% [*5315-7*
Beil. 6(3),3627 *FT-NMR* 1(2),314C

H5,680-0 **2-Hydroxypyridine,** 97% [*142-0*
★ mp 105-107° bp 280-281° *Beil.* 2
SI 396,B,7 *Safety* **2**,1958B *R&S* 1
Catalyst for generating β-oxopro
alcohols' and in the aminolysis o
1993, 1749. (2) *Polymer* **1994**, *35*,

H5,700-9 **3-Hydroxypyridine,** 98% [*109-0*
★ *Fieser* 1,486 *FT-NMR* 1(3),279B
R&S 1(2),2515F *RTECS#* UU7701

12,061-8 **4-Hydroxypyridine,** 95% [*626-0*
★ *Beil.* **21**,48 *FT-NMR* 1(3),279A *F*
R&S 1(2),2515D *RTECS#* UU7701

2-Hydroxy-5-pyridinecarboxyli page 830

3-Hydroxy-2-pyridinecarboxyli page 834

6-Hydroxy-2-pyridinecarboxyli page 834

α-Hydroxy-2-pyridinemethane 2-Pyridylhydroxymethanesul

3-Hydroxy-2-pyridinemethano (hydroxymethyl)pyridine hyd

44,754-4 **2-Hydroxypyridine-*N*-oxide,** s
[*40043-22-9*] FW 133.08 n_D^{20} 1.3

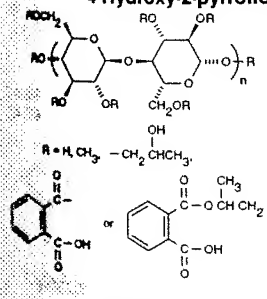
12,252-1 **3-Hydroxypyridine *N*-oxide,** 9
mp 190-192° *FT-IR* 1(2),915B *SI*
RTECS# UU7719100 *HYGROSC*

4-Hydroxy-2-pyridone, see 17,

H5,740-8 **2-Hydroxypyrimidine hydroch**
★ hydrochloride) FW 132.55 mp
R&S 1(2),2563O *HYGROSCOPIC*

4-Hydroxypyrimidine, see 85,

4-Hydroxy-2-pyrrolidinecarbo



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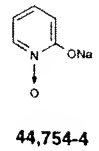

44,754-4